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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/293,670	04/16/1999	JOSEPH FISHER	A-68104/DJB/	5176

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/293,670	FISHER ET AL.	
	Examin r	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/24/04 has been entered.

Status of Claims

Claims 17-20 are under examination.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide

enablement for a method using a library of any bioactive agents that modulates any population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons advanced in the previous Office actions and reiterated as follows:

The scope of enabling disclosure provided in the specification is not commensurate in scope with the recited method. The method employs broadly any type of library of bioactive agent that affects any type of cell population. The specification provides only broad generalized statements. However, the exemplification is drawn to a single bioactive agent, p21 for a particular type of cell population, tumor. It is not apparent from the single example how the p21 has been considered a candidate for a bioactive agent since the nucleic acid encodes specifically said p21, not from a library. It would take an undue amount of experimentation for one skilled in the art to determine incalculable parameters included in the broadly claimed scope. The factors that are to be considered in the determination of undue experimentation are disclosed in *In re Wands,* (U.S.P.Q. 2d 1400 (CAFC 1988). These include: the quantity of experimentation necessary, the amount of direction

or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to readily go about determining the bioactive agent(s) present in a library of unknown compounds, whether said bioactive agents present in the library are identical or different, the number of said bioactive agents comprise in the library, the method of screening or determining as whether a bioactive agent is a candidate for cell population reaction, the size of the library comprising a different bioactive agent, the altering effect of the bioactive agents on the phenotype of the cell population, the type of cell population that can be altered by a bioactive agent, the more than five different parameters that can be measured by FACS and other unpredictable effects. Furthermore, the specification does not provide adequate direction with regards to the library of nucleic acid encoding said bioactive agents or the expression package of the nucleic acid; where one can make insertions in an expression system so as not to cause deleterious effects on the viral vector. If the expression vector use is a viral vector, there is no direction and guidance concerning how to determine which sites will not affect the viral life cycle such as the ability of the virus to

attach and enter a cell. The nucleic acid fusion libraries may contain so many inserts per viral vector that the synthesis of the inserts produces an observable effect on the host metabolisms. Because of this, there is very significant censorship of the library due to a broad set of selection factors ranging from proteins synthesis to virion assembly.

2). Applicants have failed to provide any working examples for any library of bioactive agent or nucleic acid in any retroviral vector transfected into any organisms such as virus, yeast or bacteria.

3). The state of the prior art is such that the consequences of some bioactive agent and cell interaction on some cells have not yet been fully determined or elucidated. See Polyak (Genes and Development) at e.g., page 1945, col. 2.

4). The art is inherently unpredictable with respect to the numerous types of bioactive agent that alters a given cell population, the vectors use in nucleic acid expression or display wherein even if one surface protein is identified as a candidate bioactive agent it is not possible to predict what effect the insertion of other bioactive agent into the viral protein will have on the agent or the vector package *a priori*. Also, the use of a wide variety of libraries with bioactive agent presentations can be displayed in an extraordinarily large

number of conformations. See Luo (Nature) e.g., at page 159, col. 2, first incomplete paragraph. Nakanishi(The EMBO Journal) e.g., at page 556, col. 2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2.

5). The breadth of the claims encompasses a large possible combinations for the different recited variables such as the large diversity of bioactive agent or nucleic acids that encodes said bioactive agent and cell population.

6). While the level of skill in the art is high, the molecular biology and gene art is so unpredictable that it would require undue experimentation to make the invention commensurate in scope with that claimed in the absence of adequate guidance or direction as set forth above.

Response to Arguments

Applicants submit that Applicants' specification provides a large number of examples of candidate agents which may be used in the methods of the invention, as well as methods and sources for obtaining and producing these candidate agents (see, for example, page 16, line 8 through page 30, line 15). In particular, the instant invention includes providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents for use in the claimed methods. Applicants' specification provides detailed

description of making and using libraries of retroviral vectors encoding candidate bioactive agents and methods for introducing these vectors into cells (see, for example page 19, line 31 through page 31, line 4).

In reply, a review of the relevant sections e.g., page 16, line 8 up to page 30, line 15 only provides a definition for the term "candidate bioactive agent". That is any molecule, e.g., protein, small organic molecule, carbohydrates (including polysaccharides), polynucleotide, lipids, etc. Applicants' disclosure would not enable a skilled artisan to carry out the claimed methods without undue experimentation given only the broad definitions of the components used in the method. It is not apparent which of these broad components can be combined or employed in the method to accomplish the claimed method.

Applicants point out that the instantly claimed methods are used to identify compounds that have a desired effect on preselected parameters to be measured. The methods of the invention do not require that the agent that causes the different cellular phenotype parameters be identified prior to performing the assay. In fact, the purpose of the assay is to Identify the agent, which causes an effect on cellular phenotype, as determined by sorting the cells based on at least five different parameters. For the purposes of such an assay, it

is not required that the identity of a candidate agent be known at all, let alone prior to performing the assay.

In response, the claims recite detecting an altered phenotypic cell not identifying compounds that have the said effect. Assuming that the cell phenotype equates to the identification of the bioactive agent, as argued, however, it is not apparent from the disclosure which agent effects a cell phenotype in at least more than five ways. More importantly, as to how the FACS measured the more than five parameters, simultaneously. The guidance provided in the disclosure i.e., Examples, appear to recite already a known agent that affects a cell population and sorting the cell by at most three phenotype alterations. Furthermore, as acknowledged by applicants above, the candidate bioactive agents include numerous types of agents. It is well known in the art that agents especially of unknown structure or constitution when made into a library may not provide a true representation of the candidate agents in the library. More importantly how the agents affect the cell phenotype in a number of ways as recited. It is not therefore apparent from the enabling disclosure which bioactive agent can be considered candidate to affect the cell phenotype. Mere recitation of a method with any agent would appear as to the method being manipulatively affected by the compound agent.

There are too numerous undefined variables for one skilled in the art to determine in order to practice the claimed invention. To select and determine the various agents that would affect a cell phenotype in five different ways amounts to an invitation to experiment. Before measurement of even a single effect is achieved, one has to identify the source (agent) that causes the different cellular phenotype parameters. Because the art is so highly unpredictable, specifically the library of bioactive agents such as peptide, carbohydrates, lipids, DNA or combinations thereof, one cannot make prophetic statements, absent experimental studies. Accordingly, to determine the numerous possible combinations of each of the broadly recited parameters encompassed by the claims requires undue experimentation. The claimed invention is nothing more than an invitation to experiment.

Applicants submit that the Patent Office has recognized that screening assay claims having no limitation as to the compounds to be tested are patentable (see, for example U.S. Patent No. 6,461,813, which was cited by the Examiner in the instant Office Action).

In reply, it is well settled that each case must be determined on its own facts.

Double Patenting

Claims 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Application No. 09/157,748 (now U.S. Patent No. 6,461,813) or over application S.N. 09/062,330 for reasons of record.

Response to Arguments

Applicants state that at such time as the subject matter of the provisionally rejected claims is allowed in the '330 or '748 applications, Applicants will terminally disclaim the corresponding claims of the present application.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 17-20 are rejected under 35 U.S.C. 103(a) as being obvious over Application No. 09/157,748 (now U.S. 6,461,813) which has a common inventor with the instant application for reasons advanced in last Office action.

Applicants respectfully submit that claims 1-7 were canceled in the previous Amendment and Response, filed January 17, 2002, thereby rendering the foregoing rejection moot.

In response, this rejection is applied to the present claims 17-20 (added after the cancellation of claims 1-7).

In the absence of the 132 declaration the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-20, as amended, are rejected under under 35 U.S.C. 103(a) as being obvious over Nolan (WO 97/27212) in view of Jia-ping (Chinese Journal of Physical Medicine) or Ryan et al (Jrnl. of Immunological Methods).

Nolan discloses a method of screening for a bioactive agent capable of altering a cellular phenotype of a cell which comprises combining at least bioactive agent and a population of cell or introducing a library of nucleic acids encoding a candidate bioactive agents into a population of cells and sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters. Nolan further discloses other phenotypic changes of cells that can be sorted

out based on these changes using FACS. Note e.g., page 3, lines 6-13; page 4, lines 26-27; page 14, lines 15-22; page 18, line 30 up to page 19, line 17; page 23, line 19 up to page 24,line 6; page 28,lines 25-29; page 29, line 8 up to page 30, line 16; page 31, line 7 up to page 32, line 6; page 33,lines 19-28; page 34,line 10; Example 4, page 73 up to page 80. Nolan does not disclose a method in which the cellular phenotype is exocytosis. However, Jia-ping discloses exocytosis a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increased of purity of the divided cell and further information of different cell subpopulations that can be obtained (page 1).

Ryan discloses that gating on log 90 degree light scatter (i.e., exocytosis) and log red fluorescence reduced the incidence of nonspecific binding using multiple flow cytometric parameters, page 115 and pages 120, Table 1 up to page 127. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the exocytosis phenotype change in the method of Nolan in the manner as taught by either Jia-ping or Ryan for the advantages each taught by Ryan or Jia-ping, above, in the measurement of said exocytosis change in a cell population in a multi-parameter analysis.

Response to Arguments

Applicants acknowledge that the Nolan reference broadly discusses methods for isolating a cell having an altered phenotype from a plurality of other cells (see, e.g., page 33, lines 19-28 of the Nolan reference). For example, Nolan discloses that standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS may be used in detecting an altered cellular phenotype (page 31, line 32 through page 32, line 1 of the Nolan reference). Nolan also describes the use of FACS to measure b-gal expression (page 76, lines 14-21), lacz expression (page 28, lines 27-30), and to select for cells that induce VCAM or ICAM-I expression and IL-I signaling (page 79, lines 1 8-20). But argue that there is no teaching or suggestion in Nolan, et al. to do multiple analyses, let alone measuring at least five parameters to identify an alteration in cellular phenotype, wherein the cellular phenotype is selected from the following: cell cycle, apoptosis, exocytosis, expression of a cell surface receptor, and expression of a reporter gene. Nolan refers to only to assaying a single phenotype per assay, not on at least five parameters. Applicants submit that Example 1 does not describe the sorting of cells based on at least five parameters.

Rather, Example 1 describes the screening of cells based on the fluorescence of fluorescein labeled dUTP. Furthermore, Nolan does not teach or suggest providing a population of cells comprising a library of retroviral vectors encoding different candidate bioactive agents and sorting the cells based on at least five parameters using FACS.

In reply, Example 1, line 23 up to page 52, line 2 does not measure only one phenotype. Example 1, page 51 uses FACS to analyze a fluoresceinated cell, expression of the cells, apoptosis inhibition, use of dye techniques as propidium iodide or other dyes such as ethidium bromide/acridine orange. Furthermore, Nolan at page 33, lines 19-28 Nolan describes that once a cell with an altered phenotype is detected, the cell is isolated from the plurality, which does not have altered phenotypes. This is done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include FACS, expression of survival protein, (cell cycle, as claimed) induced expression of a cell surface protein(expression of a cell surface receptor, as claimed) or other molecule that can be rendered fluorescent or taggable for physical isolation, death of cells (apoptosis) and isolation of DNA or other cell viability indicator dyes etc.

Thus, this suggested teachings of Nolan of the different means by which a cell phenotype can be detected or sorted can suffice the finding of obviousness. Each of Ryan and Jai-ping provides the motivation to do a multi-parameter analysis using at least five parameters. These parameters are disclosed or at least suggested by Nolan.

Applicants' arguments with respect to Kamb and Hide are moot in view of the new grounds of rejection above.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw

January 7, 2005